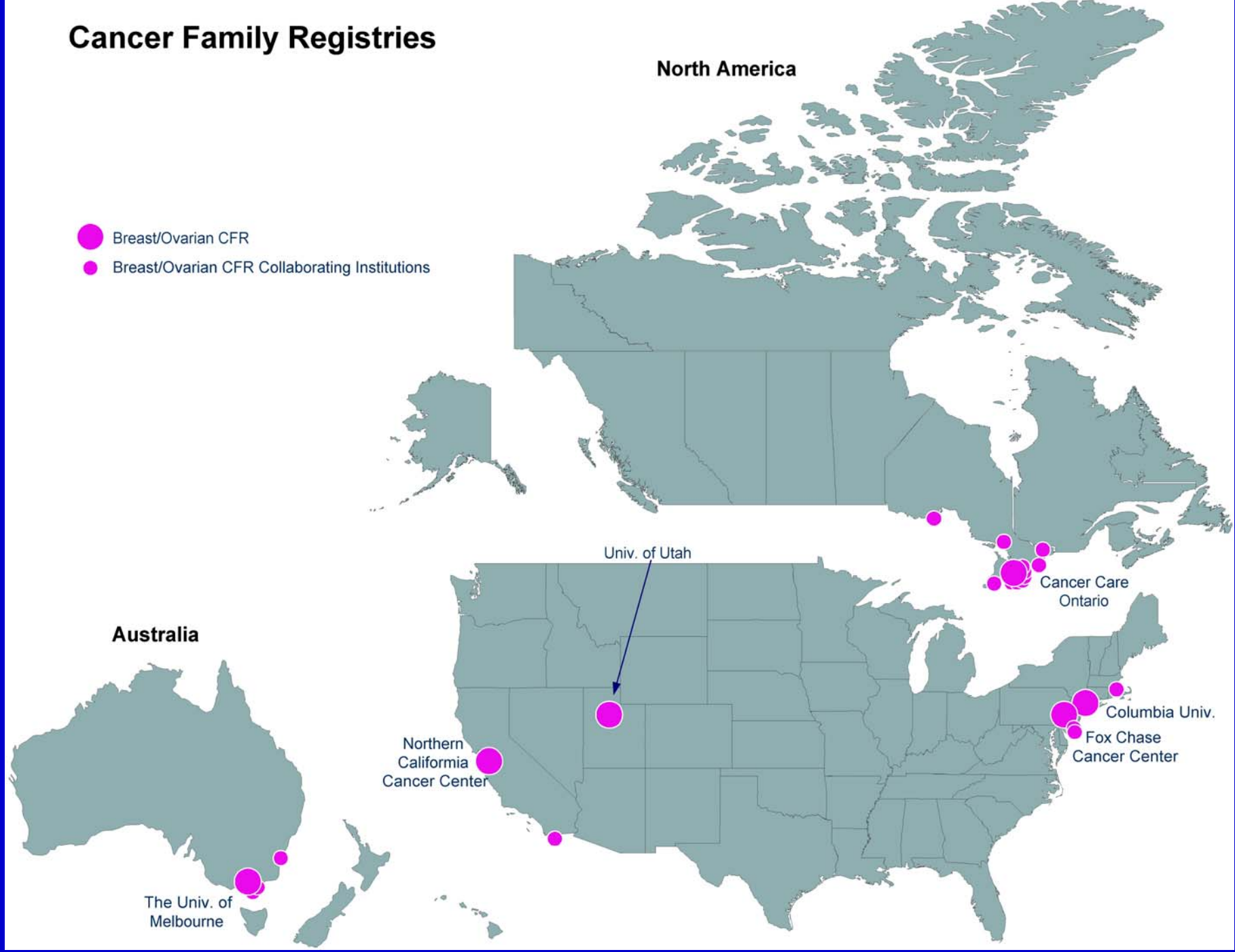
Breast Cancer Family Registry:
Overview of Progress and Scientific Agenda

Cancer Family Registries



Major Research Themes

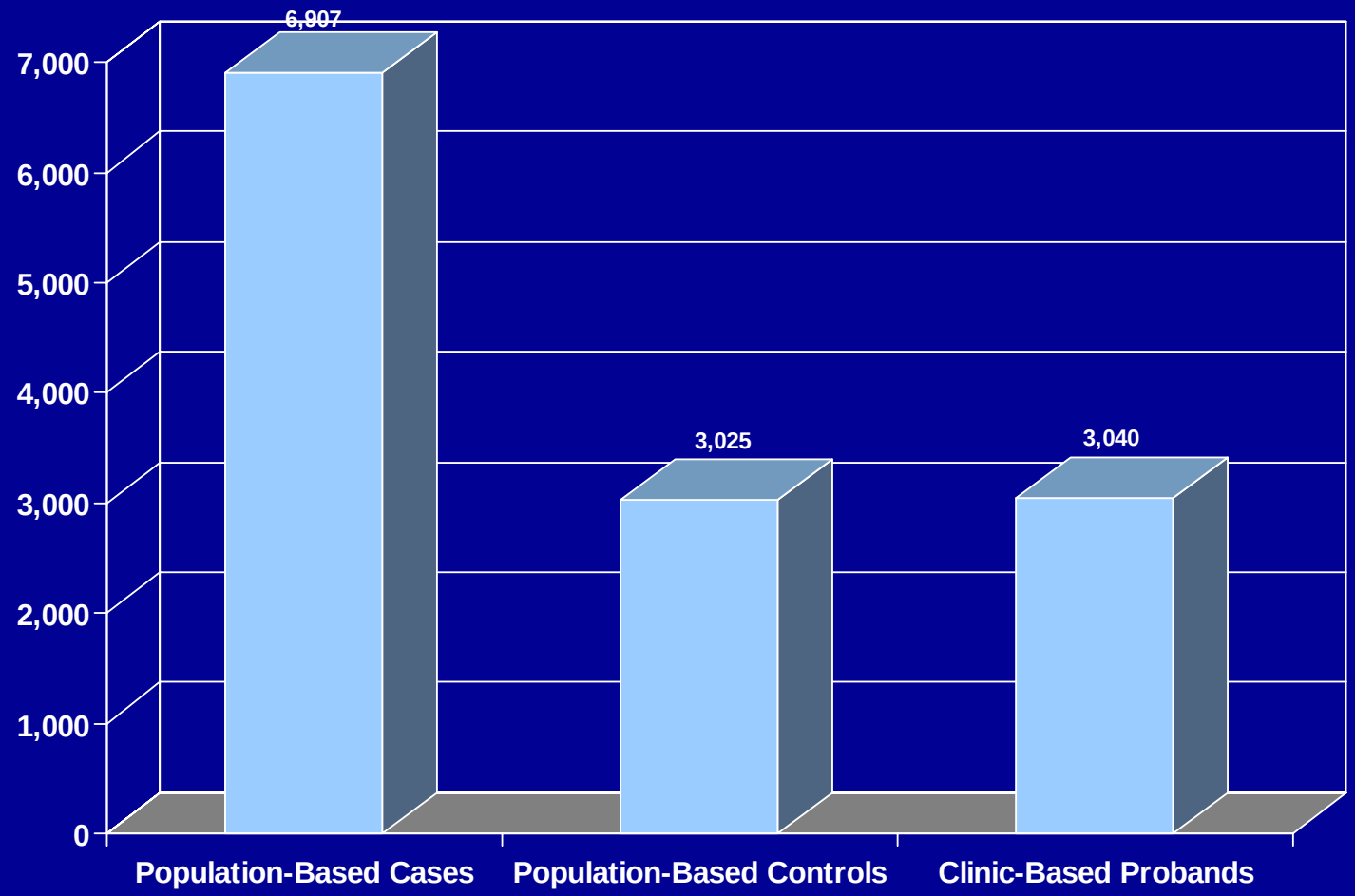
bi-directional continuum of research from basic biology to clinical practice

- Identification of genetic factors related to breast cancer risk
- Investigation of environmental modifiers of genetic risk
- Translational and clinical research
- Behavioral response to familial breast cancer

Unique Features of Breast CFR

- Collection of a large number of families across a wide range of breast cancer risk ascertained through
  - clinic-based sampling
  - population-based sampling
  - population controls
- Large collection of
  - minority families
  - Ashkenazi Jewish families
  - early-onset families
  - multiple-case families
  - *BRCA1* and *BRCA2* mutation carrier families
    - BCFR, KConFab, OCGN

Number of Probands



Data and Biospecimens

(1995-2005)	**Affected participants**	**Unaffected participants**
Epi Q	10,494	20,612
Diet Q	8,667	9,517
Blood	8,609	13,275
Lymphoblast lines	5,491	3,020
Tissue blocks	4,986	NA

Populations Enriched in the BCFR

- Minority families
  - 896 African-American
  - 1107 Hispanic
  - 1565 Asian
- 1688 Ashkenazi Jewish
- 2666 early-age of onset (<40 yrs)

Some Other Family Characteristics

- Range of family history of probands
  - 3406 with 1 affected 1st degree relative
  - 800 with $\geq$ 2 affected 1st degree relatives
- Sister pairs
  - 1743 with 1 affected, 1 unaffected
  - 729 families with $\geq$ 2 affected sisters
- Ovarian probands
  - 45 less than 40 years
  - 169 over 40

Funding for BRCA1 And BRCA2 Genotyping

- Ashkenazi Jewish supplement
- BRCA1 RO1 (Li)
- Molecular characterization supplement
- CDC supplement
- Sites own funding

BRCA1 And BRCA2 Genotyping

- Validation of methods (Andrulis et al)
- 9,783 total participants tested
- 1,443 Mutation carriers
  - 816 affected carriers
  - 627 unaffected carriers
- Of the mutation carriers
  - 890 BRCA1 carriers
  - 553 BRCA2 carriers

Working Groups

- Analytic
- Ashkenazi
- Behavioral
- Biospecimens
- Biospecimens Access
- Case-Control
- Clinical Research
- Diet & Nutrition
- Environmental Modifiers
- Follow-up
- Legacy
- Minorities
- Molecular Characterization & Gene Discovery
- Pathology
- Polymorphisms
- Prognostic
- Publications
- Technical

Research Studies

- 120 projects approved by the AC
  - increase in multiple-site projects over time
  - currently 55 multiple-site
- provided over 72,000 DNA specimens
- provided 361 cell lines
- 66 data modules to external investigators
- R01s and other peer-reviewed funding
- projects presented in this session and posters

Collaborative Projects (R01s)

- Environmental Modifiers in BRCA1/2 Mutation Carriers (PI:Whittemore)
- Prognosis and Pathology of Hereditary Breast Cancer (PI:Goodwin)
- Mammographic Densities and Familial Breast Cancer (Rommens et al.)
- The Role of the ATM gene in familial breast cancer (Chenevix-Trench et al.)

Case- control and Environmental Modifiers WGs

- No evidence that use of current low-dose oral contraceptives increases risk of early-onset breast cancer in mutation carriers (Milne et al)
- Smoking and risk of breast cancer in carriers (Boyd et al.)
- Inverse association between ovarian cysts and breast cancer (Knight et al)
- Alcohol and breast cancer risk in carriers (McGuire et al.)

Early-age of onset Breast Cancer

Findings:

- <10% of early-onset breast cancer attributable to *BRCA1/2* germline mutations (Hopper et al)
- Subgroup of women at high risk but not due to *BRCA1/2* mutations (Dite et al)

- Current projects:
  - Further characterization of BRCA1 and BRCA2
  - Gene discovery
  - Genome wide scans (Ahsan etal)
  - Candidate gene approaches

Further Characterization of BRCA1

- Large genomic deletions (Southey et al)
- Collaborative studies on unclassified variants (Couch, Tavtigian,et al)

Gene Discovery

- Other Breast Cancer Susceptibility Genes
- Linkage methods
  - Collaborations with other groups to identify BRCAX (Goldgar and colleagues)
- BAC array comparative genomic hybridization (CGH)

Minority Studies

- Current studies
  - Comparison between African Americans in California and Nigerian women
  - IGF pathway and breast cancer risk in African Americans
- Future research (John et al)
  - Estrogen metabolizing genes
  - Oxidative stress genes
  - Unclassified variants in *BRCA1* and *BRCA2*
  - *BRCA1* and *BRCA2* studies including gene-environment interactions
  - Polymorphisms and racial/ethnic groups
  - Behavioral and psychosocial aspects of minority populations and breast cancer

Pathology Results

- Inter-observer validation study of pathology review process (Longacre et al.)

- Differences in tumor characteristics of *BRCA1* associated tumors and *BRCA2* associated tumors (Bane et al.)

Genetic Variation/Polymorphism Studies

- B-CFR studies focusing on polymorphisms and biological pathways including:
  - Carcinogen metabolism
  - Steroid hormonal biosynthesis and metabolism
  - DNA repair
  - Oxidative stress
  - IGF
  - TGF-beta (Pasche et al)
  - Cell cycle
- External researchers examining medium-penetrance genes (*ATM* and *CHEK2*) and breast cancer risk (Bernstein, et al)

Behavioral studies

- Consent process

- Personal risk perception and screening behaviors among Ashkenazi Jewish population (Apicella et al)

- Ethno-cultural studies (Daly et al)
  - Cultural determinants of
    - cancer risk attribution
    - understanding of genetic contribution of cancer

Renewal - Infrastructure Platforms

- Follow-up
- Targeted recruitment and expansion
- Clinical/Translational
- Biospecimen
- Pathology
- Molecular
- Analytic/Informatics
- Behavioral/Survivorship
- Administration

Follow-Up Goals

- Obtain outcome data (recurrence, morbidity, death) for affected and unaffected participants
- Update information on relevant lifestyle, clinical and environmental exposures.
- Obtain current breast and ovarian cancer status of first- and second-degree relatives.
- Enable the collection of additional biospecimens
- Enable the study of screening and other behaviors, beliefs, attitudes and knowledge of breast cancer control efforts of cohort members.
- Request permission to obtain recent mammograms for future breast density studies.
- Obtain up-to-date contact information on participants

Targeted Enhancement Goals

- Recruit additional minority families.
- Enhance the resource with additional *BRCA1* and *BRCA2* carrier families.
- Expand the families with early-onset breast cancer.
- Expand the number of *BRCA1* and *BRCA2* negative high-risk families.

LEGACY

Lessons in Epidemiology and Genetics of Adult Cancers from Youth

- youth cohort
- collect biospecimens, epi data, etc
- studies: polymorphisms, epi, behavioural, etc
- collect diet, exercise data
- serum markers, biological endpoints

Clinical Platform Goals

- Expand data collection on pathologic and clinical prognostic factors, treatment and outcome.
- Expand data collection on epidemiologic prognostic factors.
- Expand data collection on previous screening activities.
- Expand data collection on preventive measures, such as chemoprevention and surgical intervention.
- Identify candidates from high-risk families to be readily available for clinical research protocols of screening and prevention.

Biospecimens: Goals

- Maintenance of the current resource and continued distribution of samples
- Enhancement of the resource by
  - collection of materials
  - establishment of cell lines
  - preparation of DNA from relatives
  - establishment of cell lines and preparation of DNA from controls
  - complete quality control
- performing applied research relevant to the resource materials
- Consolidation and centralization

Pathology Platform Goals

- Enhance an integrated and coordinated pathology review process
- Develop TMAs from the tumors in the BCFR
- Establish a virtual Hematoxylin and Eosin (H&E) repository

Molecular Platform Goals

- Complete *BRCA1* and *BRCA2* testing
- Extend for select groups the current *BRCA1* and *BRCA2* characterization and analysis by performing tests for missense mutations, large genomic alterations and other emerging tests.
- Test carrier family members for family specific mutations.

Analytic Platforms Goals

- Work with the IC to ensure that internally consistent, high quality data are organized efficiently and conveniently.
- Facilitate the orderly, systematic use of this database by a large group of interdisciplinary investigators.
- Assist with study design issues as needed
- Insure uniform description of data, methods and analysis in future publications

Behavioral/Survivorship Goals

- Make available consultation to interested investigators
- Maintain a core resource library
- Make available a catalogue of relevant theoretic models with indications for use in a wide spectrum of research settings
- Make available a catalogue of automated programs for questionnaire scoring, qualitative and quantitative statistical analyses.
- Provide established intervention protocols
- Implement a Health Related Quality of Life Measurement.

Core Platforms & Related Research Themes

Platforms

- Behavioral Response to Risk
- Environmental Modifiers
- Identification of Genetic Modifiers
- Translational Studies